C1 CONT.

ID NO:2 (VanH), SEQ ID NO:6 (VanX), SEQ ID NO:8 (VanC), SEQ ID NO:12 (VanR), SEQ ID NO:14 (VanS), SEQ ID NO:19 (transposase), SEQ ID NO:21 (resolvase), SEQ 10 NO:23 (Van Y) and SEQ ID NO:25 (VanC).--

SUPPORT FOR THE AMENDMENT

Claims 36-42 replace Claims 29-35, respectively, and find support in the specification and original claims.

Support for the conditions of hybridization recited in Claim 41 is found on page 4, line 29, to page 5, line 1.

Support for Claim 43 is found on page 41, line 8 to page 42, line 21, and in the Sequence Listing.

No new matter would be added to this application by entry of this amendment.

Upon entry of this amendment, Claims 36-43 will now be active in this application.

REQUEST FOR RECONSIDERATION

Applicants wish to acknowledge the interview held on November 1, 2000, between Applicants' representative and Examiners Hutson and Prouty. Applicants sincerely appreciate the Examiners' courtesy and helpful suggestions. At that time, Applicants' U.S. representative argued that the compositions of the invention are enabled by Applicants' disclosure and that the prior art does not disclose or suggest Applicants' compositions. The following is intended to expand upon the discussion with the Examiners.

The objection to Claim 34 due to the double inclusion of the terms "SEQ ID NO:9" and "SEQ ID NO:10" has been obviated by appropriate amendment. Claim 41, which replaces Claim 34, contains only a single reference to each of SEQ ID NO:9 and SEQ ID

NO:10. Since the amendment merely deletes duplicative subject matter the amendment is not a narrowing of the claims.

The rejection of Claims 29-33 under 35 U.S.C. §112, second paragraph, has been obviated by appropriate amendment. Applicants' amendment of the term "or a combination thereof" to --and a combination thereof-- is not a narrowing of the claims.

Applicants have rewritten Claim 29 as new Claim 36, and possible ambiguity related to the use of the term "combination thereof" has been avoided.

Furthermore, Applicants have rewritten Claim 34 as new Claim 41, wherein it is stated that the hybridization is carried out "under conditions of high stringency or only slightly stringent conditions", which conditions are fully defined on page 4, line 29 to page 5, line 1, of the specification.

In view of Applicants' amendment, withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

The rejection of Claim 34 under 35 U.S.C. 112, first paragraph, is obviated in part by appropriate amendment and is traversed in part.

The Examiner has articulated that there is insufficient enablement for the full scope of the compositions encompassed by Claim 34 which, he argues, encompasses many functionally unrelated polypeptides.

The claims have been amended to address these issues. In new Claim 41, the fragments of proteins depicted by SEQ ID NO: ID NOS: 2, 4, 6 and 25 are now claimed, functionally, by their ability to confer resistance to glycopeptides in Gram-positive bacteria. Similarly, the proteins or fragments thereof encoding a sequence which is able to hybridize with SEQ ID NO: ID NOS:7, 8, 9 and 10 are also defined, functionally, by their ability to confer resistance to glycopeptides in Gram-positive bacteria.

The present results clearly show that the expression of the *vanA, vanC, vanH* and *vanX* genes confer resistance to glycopeptides in Gram-positive bacteria. Furthermore, the specification clearly describes the construction of plasmids containing different fragments of the claimed nucleotide sequences (page 24, line 26 *et SEQ ID NO:*.) and the assay for resistance to vancomycin (page 30, lines 9-11). Applicants respectfully submit, therefore, that the preparation of (a) a composition comprising a VanA, VanC, VanH or VanX protein, and a protein encoded by a fragment of these genes which retain the ability to confer resistance to glycopeptides in Gram-positive bacteria, and (b) a composition comprising a protein or fragment thereof which encodes a sequence which is able to hybridize with SEQ ID NO: ID NOS:7, 8, 9 and 10, wherein the protein or fragment thereof are defined, functionally, by their ability to confer resistance to glycopeptides in Gram-positive bacteria, is enabled to those of ordinary skill in the art without undue experimentation.

The Examiner has also articulated that the present invention lacks additional representative species encompassed by the claimed compositions. The Applicants respectfully disagree with the Examiner's conclusion. One **variant** of the *vanA* gene, ***vanC,*** is described on page 37, line 1, *et SEQ ID NO:*. of in the specification. Applicants' data clearly show that the *vanC* gene which was identified by using a probe from the *vanA* gene, encodes a protein which is necessary for resistance to vancomycin in *Enterococcus gallinarum* BM4173 (see page 39, lines 14-31). Therefore, at least one example is given in the specification that describes a representative species of the claimed compositions, and such data provides further guidance to those of ordinary skill in the art to enable them to practice the claimed invention without undue experimentation.

In the light of the above amendment and remarks, Applicants therefore respectfully request that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and

withdrawn.

The rejection of Claims 29 and 34 under 35 U.S.C. §102(b) as being anticipated by Dukta-Malen et al. (*Mol. Gen. Genet.* 224: 364-372, Dec 1990) is respectfully traversed.

Preliminarily, the Examiner acknowledged during the aforementioned interview that the rejection erroneously referred to Claim 29, when only Claim 34 was intended to be included in the rejection under 35 U.S.C. §102(b).

Furthermore, the Dukta-Malen et al. reference is unavailable as prior art. The Applicants have filed a Request for Priority in the present application for the benefit of the filing date of their French priority document, French Application No. 9013579, which has a filing date of October 31, 1990. Furthermore, a certified copy of the French priority document was submitted to the International Bureau in PCT Application No. PCT/FR91/00855. To perfect their claim to priority, therefore, Applicants submit herewith an English translation of French Application No. 9013579. In view of the above, since the reference is not available as prior art, the rejection is believed to be improper and should be withdrawn.

The rejection of Claim 34 under 35 USC §102(b) as being anticipated by ICN Biomedicals, Inc.Catalog is respectfully traversed.

The ICN Biomedicals,Inc.Catalog reference lists the amino acid alanine as well as alanine linked to other amino acid residues. The reference does not disclose a composition comprising VanH, VanA, VanX and VanC proteins having the amino acid sequences depicted in SEQ ID NOS: 2, 4, 6 and 25, respectively, nor fragments of these proteins which retain the ability to confer resistance to glycopeptides in Gram-positive bacteria. The reference also does not disclose proteins or fragments thereof which are able to hybridize to SEQ ID NOS:7, 8, 9 and 10 under the recited conditions. Accordingly, the invention of

Claim 41 is clearly novel and not obvious from the cited prior art of record. Withdrawal of the rejection under 35 USC §102(b) is therefore respectfully solicited.

The rejection of Claim 34 under 35 U.S.C. §103 (a) as being unpatentable over Brisson-Noël et al. (*Antimicrobial Agents and Chemotherapy,* 34(5):924-927, May 1990) is respectfully traversed.

The claimed invention is not obvious over the cited reference as the prior art fails to disclose or suggest a composition comprising any one of the proteins VanH, VanA, VanX or VanC which have the amino acid sequences depicted in SEQ ID NOS: 2, 4, 6 and 25, respectively, nor a composition comprising a fragment of one of these proteins which retains the ability to confer resistance to glycopeptides in Gram-positive bacteria. The reference also does not disclose or suggest a composition comprising a protein or fragment thereof which is able to hybridize to SEQ ID NOS:7, 8, 9 and 10 under the conditions recited in the claims.

Brisson-Noël et al. describe 4 kb- and 6 kb-*EcoR1* fragments of a plasmid pIP816 which confer high-level glycopeptide resistance in *Enterococcus faecium* BM4147. The 4 kb fragment harbors a vanA determinant which confers resistance to glycopeptides in Gram-positive bacteria. The reference does not describe the nucleotide or amino acid sequences of the vanA determinant, nor does it suggest mechanisms to explain the observed resistance to glycopeptides associated with the plasmid pIP816. Rather, the reference teaches that it is **not** possible to identify the exact nature of the determinant present on the 4 kb fragment since "**additional sequences present on the 6 kb *EcoR1* fragment appear to be required for full expression of the glycopeptide resistance phenotype**...". (Page 925, left col., lines 11-16) (Emphasis added by Applicants).

In contrast, the invention of Claim 41 relates to a composition comprising (a) a VanH, VanA, VanX or VanC protein having the amino acid sequences depicted in SEQ ID NOS: 2,

4, 6 and 25, respectively, or a fragment of these proteins which retains the ability to confer resistance to glycopeptides in Gram-positive bacteria, or (b) to a protein or fragment thereof which is able to hybridize to SEQ ID NOS:7, 8, 9 and 10 under the recited conditions, and which has the ability to confer resistance to glycopeptides in Gram-positive bacteria.

The Examiner has articulated that the reference disclosure of a vanA determinant renders obvious Applicants' composition comprising a VanA protein. How can Applicants' composition be obvious when the closest prior art of record not only fails to **describe** a gene which encodes a glycopeptide resistance protein, but does not disclose any nucleotide or amino acid sequences which correspond to a protein conferring resistance to glycopeptides in Gram-positive bacteria?

The cited reference clearly fails to disclose the claimed compositions. In addition, since the exact nature of the vanA determinant disclosed in the reference is unclear, there is no motivation to isolate a VanA protein, or to determine the amino acid sequence of the protein. Furthermore, since the prior art does not disclose whether the vanA determinant even corresponds to a gene involved in the expression of the resistance phenotype there is also no expectation of successfully obtaining a VanA protein which confers resistance to glycopeptides in Gram-positive bacteria.

In view of the deficiencies of the art, the claimed invention is not *prima facie* obvious and accordingly, withdrawal of the rejection under 35 U.S.C. §103 (a) is respectfully requested.

Applicants respectfully submit that the present application is now in condition for allowance and early notice of such action is earnestly solicited.

Respectfully submitted,

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